

Role of ca 19-9 as a tumor marker in diagnosis and prognosis of pancreatic carcinoma and cholangiocarcinoma (A study of 46 cases)

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Abstract

Introduction: Ca19-9 is currently the single most useful tumor marker for diagnosis and prognosis of pancreatic cancer and cholangiocarcinoma. **Aim:** The aim is to elucidate the importance of tumor marker ca 19-9 as a diagnostic and prognostic tool in pancreatic carcinoma and cholangio-carcinoma. **Material and Methods:** The time period of the study was from september-2012 to september- 2014. The patients were investigated pre-operatively and post operatively for ca 19-9 levels in their serum with the use of ELISA (enzyme linked immunosorbant assay) test. **Results:** Total 28 cases of pancreatic lesions were considered which included 24 cases of pancreatic ductal adenocarcinoma, It was observed that when preoperative serum CA 19-9 level was less than 37 u/ml median survival was 28 months. However when CA 19-9 level was more than 200 u/ml, median survival was 6 months. Out of 18 cases studied in gallbladder tumors, 15 cases were of cholangiocarcinoma. Patients with pre-therapy serum CA 19-9 level was between 37 -200 u/ml median survival was 23.25 months. When CA 19-9 level was more than 200 u/ml, median survival was 10.25 months. **Conclusion:** Elevated level of ca 19-9 in pancreatic carcinoma and cholangiocarcinoma are associated with higher age group, male sex, higher histological grade, higher TNM staging and metastasis. Post operative ca 19-9 value has definitive prognostic value to detect any metastasis or recurrence in pancreatic carcinoma and cholangio- carcinoma. Therefore it can be concluded that ca 19-9 is an important tumor marker for pancreatic carcinoma and cholangio-carcinoma.

Keywords: CA19-9, Cholangiocarcinoma, Pancreatic Carcinoma, Tumor marker

Introduction

CA 19-9 although widely used for diagnosis of pancreatic carcinoma and cholangiocarcinoma there is no proper study to associate it with histological grade and TNM staging of pancreatic and cholangiocarcinoma. As a result this study was undertaken to determine the aforementioned association of CA 19-9.

CA 19-9 is underestimated in its use after curative surgery or chemotherapy of pancreatic carcinoma and cholangiocarcinoma. In this study we wanted to establish if CA 19-9 level both pre and post operatively was associated with survival rate in patients.

The CA19-9 antigen is defined by an igg1 mouse monoclonal antibody raised against the human colonic carcinoma cell line SW 1116 by Koprowski and colleagues in 1979 [1]. Although the CA19-9 antibody was generated against a colorectal cancer cell line, it is found more frequently in the sera of patients with pancreatic carcinoma [2].

CA19-9 is currently the single most useful blood test in differentiating pancreatic cancer from chronic or recurring pancreatitis with a sensitivity ranging from 70–90% and specificity from 68–91% [3-6].

CA 19-9 is one of the most significant prognostic factors for both patients with resectable and those with

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un-resectable pancreatic carcinoma and cholangiocarcinoma. [7-9].

It has been shown that elevated serum concentrations of CA19-9 decrease after curative surgery and conversely that recurrent disease is often associated with an increase in the circulating level of this serum marker, which is a prerequisite for the use in follow-up of pancreatic carcinoma and cholangiocarcinoma. [3].

Aims

To elucidate the importance of tumor marker CA 19-9 as a diagnostic and prognostic tool in pancreatic carcinoma and cholangiocarcinoma.

Basic aim of present study is to study the role of tumor marker, CA19-9 test as a diagnostic and prognostic tool in pancreatic carcinoma and cholangiocarcinoma, monitor the response to treatment both surgical as well as radiotherapy, to follow up and analyze the correlation between CA 19-9 levels and clino-pathological features like age, stage of disease, size, grading, staging and metastasis.

Material and Method

Study Design: This is a prospective study of 46 cases.

Study setting: The study was carried out in tertiary care centre affiliated with M.P. Shah Medical College. The patients were admitted in various wards like Surgery, Medicine and Radiotherapy.

Time period: The study was from September-2012 to September- 2014.

Inclusion criteria

1. Age 20years-100years
2. Both genders
3. Symptoms: Chief complaint of anorexia, malaise, nausea, vomiting, substantial weight loss, mid-epigastric pain, melena, hematemesis, dysphagia, jaundice, epigastric lump etc. Was considered with USG, CT SCAN and MRI findings.

Method used

1. These patients were investigated for CA 19-9 levels in their serum with the use of ELISA (Enzyme Linked Immunosorbant Assay) test.
2. Both Pre operative and Post operative values were measured to see the changes in CA 19-9 value after

tumor resection. Post operative value was measured after 30 days of surgical resection or 3 cycle of chemotherapy/Radiotherapy.

3. Preoperative serum Ca 19-9 level was also correlated with survival of patient.
4. Patients were followed up on regular basis through telephonic communication or/and hospital records.
5. Postoperative/ Post-therapy change in CA 19-9 was correlated with survival of patients.

Principle of the ca 19-9 assay:[10-20]:

1. Company's Name: **Calbiotech CA 19-9 Elisa**
2. The CA19-9 ELISA test is based on the principle of a solid phase enzyme-linked immunosorbent assay. The assay system utilizes a monoclonal antibody directed against a distinct antigenic determinant on the intact CA19-9 molecule is used for solid phase immobilization (on the micro-titer wells). Another CA 19-9 monoclonal antibody conjugated to horseradish peroxidase (HRP) is in the antibody-enzyme conjugate solution.
3. The concentration of CA19-9 is directly proportional to the colour intensity of the test sample. Absorbance is measured spectrophotometrically at 450 nm.

Specimen collection and handling: [10-20]

1. Collect blood specimens and separate the serum.
2. Specimens may be refrigerated at 2–8°C for up to seven days or frozen for up to six months.
3. Avoid repetitive freezing and thawing of serum sample.

Calculations and results: [10-20]

1. Calculate the average absorbance values (A450) for each set of reference standards, control, and samples.
2. Construct a standard curve by plotting the mean absorbance obtained for each reference standard against its concentration in U/ml via best fit quadratic on linear graph paper, with absorbance on the vertical (y) axis and concentration on the horizontal (x) axis.
3. Using the mean absorbance value for each sample, determine the corresponding concentration of CA19-9 in U/ml from the standard curve.

Reference value [10-20]

1. Healthy men and women are expected to have CA19-9 assay values below 35 U/ml.
2. The minimum detectable concentration of CA19-9 in this assay is estimated to be 10 U/ml.

Observation and Result

Pre-operative CA 19-9 was measured in every case for the purpose of diagnosis. In some cases, post-operative CA 19-9 was measured and the patient was followed up for the length of the study to determine the prognosis and survival rate.

Table-I: Demographic factors of pancreatic lesions and gall- bladder lesion

		Pancreatic lesions	Gall bladder lesions
Total no of cases		28	18
Age of pateints (in years)	20-39 years	3	0
	40-60years	14	10
	> 60 years	12	8
Sex of pateints	Male	18	11
	Female	10	7

Table-II: Types of cases considered in the study

Sr no	Types of cases	Number
1	Acute pancreatitis	2
2	Mucinous cystadenoma of pancreas	1
3	Serous cystadenoma of pancreas	1
4	Ductal adenocarcinoma of pancreas	24
5	Choledocholithoasis/gall stones	3
6	Gall bladder carcinoma/ cholangiocarcinoma	15

Table-III: Relationship between clinopathological factors and ca 19-9 values in pancreatic lesions / pancreatitis

Sr no	Clinopathological factors	Number	Ca 19-9 (mean)	Ca 19-9 (median)
1	Age : (n=28)			
	20- 39 yrs	03 (10.7%)	289.63	250.9
	40-59 yrs	14 (50.1%)	232.03	178.8
	> 60 yrs	11(39.28%)	350.20	350.2
2	Sex: (n=28)			
	Male	18 (64.28%)	395.85	218.85
	Female	10 (35.71%)	320.26	198.20
3	Location: (n=26)			
	Head of pancreas	21 (80.76 %)	445.08	253.6
	Body and tail	05 (19.23%)	173.18	193.8
5	Neoplasm: (n=26)			
	Benign	02 (14.28%)	62.35	62
	Malignant	24 (85.71%)	420.35	252.25
7	Staging: (n=24)			
	Stage i	1 (4.16%)	11	11
	Stage iia	5 (20.83%)	214.78	186.8
	Stage iib	5 (20.83%)	172.70	193.8
	Stage iii	5 (20.83%)	337.6	282.8
	Stage iv	8 (33.33%)	806.48	627.2
8	Metastasis: (n=24)			
	Only lymph node	09 (37.5 %)	617.14	362.2
	Only distant organs	04 (16.66%)	806.71	627.2
	Both In and distant organ metastasis	04(16.66%)	1339	1402.2
	No metastasis	07(29.13%)	183.92	186.8

Total 28 cases of pancreatic lesions were considered which included 24 cases of pancreatic ductal adenocarcinoma, 2 cases of acute pancreatitis, 1 case of mucinous cystadenoma of pancreas and 1 case of serous cystadenoma of pancreas.

Out of 18 cases studied in gallbladder tumors, three cases of choledocholithiasis were considered and the rest 15 cases were of gall bladder carcinoma/cholangiocarcinoma.

Table-IV: Relationship between clinopathological factors and ca 19-9 values in gall bladder tumors and choledocholithiasis

Sr no	Clinopathological factors	Number	Ca 19-9 (mean)	Ca 19-9(median)
1	Age : (n=18) 20- 39 yrs 40-59 yrs > 60 yrs	0 10(55.55%) 08(44.44%)	00 161.27 301.225	00 86.6 213.05
2	Sex: (n=18) Male Female	11(61.11%) 07(38.88%)	316.45 166.32	40 120
3	Neoplasm: (n=18) Benign Malignant	03(16.66%) 15(83.33%)	28.66 254.43	23 123.8
5	Staging: (n=15) Stage i Stage ii Stage iiia Stage iiib Stage iva Stage ivb	00 04(26.66%) 05(33.33%) 03(20%) 00 03(20%)	217.87 276.2 178.16 - 383.16	109.45 120 118.2 - 302.3
6	Metastasis: (n=15) only lymph node Only distant organs Both In and other organ metastasis No metastasis	03(20%) 01(6.6%) 02(13.33%) 09(60%)	276.34 383.16 423.6 283.6	123.8 302.2 423.6 120

Table-V: Preoperative serum ca 19-9 level co-related with survival in pancreatic carcinoma and cholangiocarcinoma

Ca 19-9 level	Median survival in pancreatic carcinoma (months)	Median survival in cholangiocarcinoma (months)
<37 u/ml	28	--
37- <200u/ml	18	23.25
>200 u /ml	6	10.25

Pre-operative serum CA 19-9 level was measured in all cases of pancreatic carcinoma and 12 cases were followed up to determine their median survival. It was observed that when preoperative serum CA 19-9 level was less than 37 u/ml median survival was 28 months.

When serum CA 19-9 level was between 37 -200 u/ml survival decreased upto 18 months. However when CA 19-9 level was more than 200 u/ml, median survival was 6 months. Thus, preoperative serum CA 19-9 level plays a role in determining survival in patients with pancreatic carcinoma.

Out of 15 cases of gall bladder carcinoma/cholangiocarcinoma, 08 cases were followed up. No case with preoperative serum CA 19-9 level <37 u/ml was followed. Patients with pre-therapy serum CA 19-9 level was between 37 -200 u/ml median survival was 23.25 months. However when CA 19-9 level was more than 200 u/ml, median survival was 10.25

months. Thus, preoperative serum CA 19-9 level plays a role in determining survival in gall bladder carcinoma/cholangiocarcinoma

Table-VI: Postoperative changes in serum ca 19-9 co-related with survival in pancreatic carcinoma and cholangiocarcinoma

Ca 19-9 level	Median survival in pancreatic carcinoma (months)	Median survival in cholangiocarcinoma (months)
>50% decrease in level	18	20
<50% decrease in level	6	13.5

Out of 24 cases of pancreatic carcinoma, 12 cases were followed up and their post-therapy changes in serum ca 19-9 level were measured. Their survival was considered according to post-operative or post-therapy CA 19-9 levels.

Out of 12 patients who were followed up on regular basis, their postoperative/ post therapy CA 19-9 value was measured and percentage of decrease in post-therapy CA 19-9 was compared with survival of patients. It was observed that when post-therapy CA 19-9 level decreases more than 50% of pre-therapy level survival rate increases and the median survival is 18 months.

However, if post-therapy decreases in CA 19-9 level is less than 50 %, they are usually patients with metastasis or reoccurrence, and their survival rate is less. Median survival for such cases is 6 months.

Out of 08 patients who were followed up on regular basis, their postoperative/ post therapy CA 19-9 value was measured and percentage of decrease in post-therapy CA 19-9 was compared with survival of patients. It was observed that when post-therapy CA 19-9 level decreases more than 50% of pre-therapy level survival rate increases and the median survival is 20 months.

However, if post-therapy decreases in CA 19-9 level is less than 50 %, they are usually patients with metastasis or reoccurrence, and their survival rate is less. Median survival for such cases is 13.5 months.

Table-VII: Statistical analysis of ca 19-9 in diagnosis of pancreatic carcinoma and cholangiocarcinoma (when cut of value for ca 19-9 is 37u/ml)

	Sensitivity	Specificity	Positive Predictive value	Negative predictive Value
Pancreatic Carcinoma	87.50%	50.00%	91.30%	40.00%
Cholangio Carcinoma	80%	66.67%	92.31%	40.00%

When cut off value for ca 19-9 value is 37 u/ml:

1) Sensitivity: it is the probability that test result will be 'positive' when disease is present. Serum ca 19-9 level is most sensitive for pancreatic carcinoma followed by cholangiocarcinoma.

2) Specificity: it is probability that the test will be 'negative, when disease is absent. This is because many benign conditions like pancreatitis show an elevation in serum ca 19-9 level (false positives)

3) Positive predictive rate: it is probability that the disease is present when test is positive.

4) Negative predictive value: it is probability that the disease is not present when the test is negative. It is 40 % for both pancreatic carcinoma and cholangiocarcinoma.



Figure-1: Gross appearance of pancreatic carcinoma showing the tumor mass protruding in tubular lumen

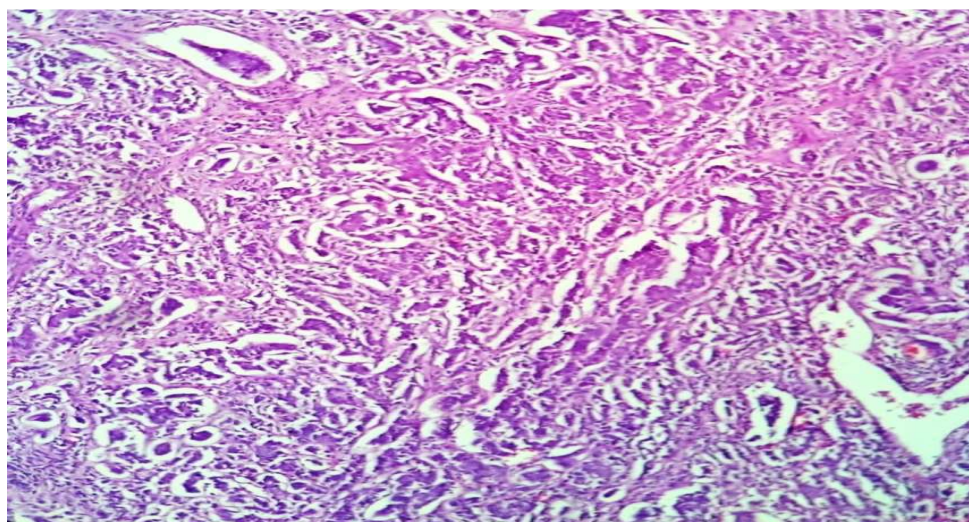


Figure-2: Histopathology of pancreatic ductal adenocarcinoma, well differentiated type (H & E X40)



Figure-3: Gross of cholangiocarcinoma showing whitish mass at neck of gall bladder

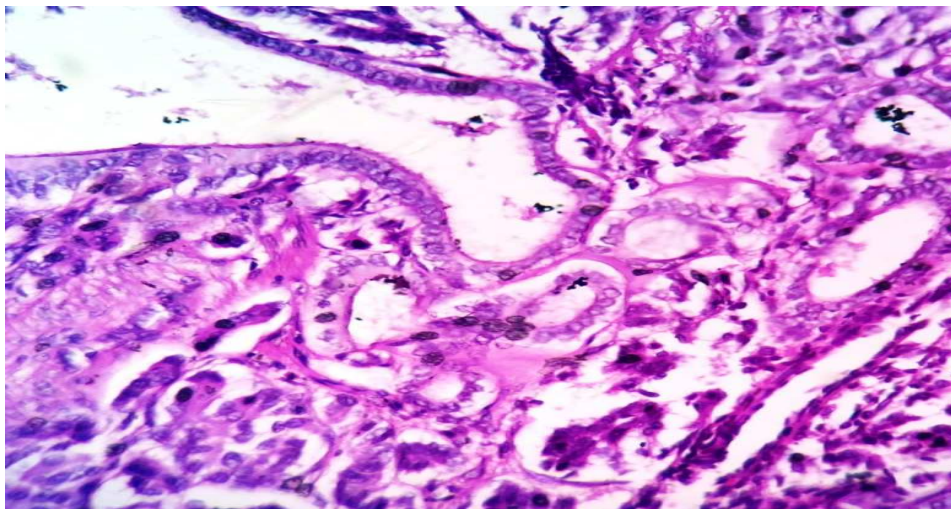


Figure-4: histopathology of well differentiated cholangiocarcinoma. (h & e x 40)

Discussion

Elisa test to measure ca 19-9 is reliable, sensitive, rapid and cost effective test. Ca 19-9 is the preferred tumor marker of choice for detection of tumor recurrence after surgery or radiotherapy in cases of pancreatic carcinoma and cholangiocarcinoma with pretreatment elevated ca 19-9. It is also a good serum marker for monitoring response to treatment for patients having pancreatic carcinoma and cholangiocarcinoma.

Pancreatic cancer- Regarding Age and sex incidence of patients pancreatic carcinoma, in the study of **dong et al [21]**, more than 50% of patients were above the age of 60 years and male to female ratio in the study was 1.2:1 while in present study 60% of patients were below the age of 60 years and male to female ratio was 1.8:1. This discrepancy in percentage was seen because of large sample size and varied age group in study of **dong et al [21]**.

The Median value of CA 19-9 was compared with staging of pancreatic carcinoma in various studies. In present study The median value of CA 19-9 for Stage Ia is 11 u/ml, Stage iia and iib is 186 and 194 U/ml respectively and Stage III pancreatic carcinoma is 282 U/ml while for Stage IV pancreatic carcinoma is 627 U/ml. Hence there is significant proportional increase in CA 19-9 with stage of pancreatic carcinoma. It was observed in all studies that the median value of CA 19-9 increased as stage of disease increases. The maximum value of CA 19-9 was observed in Stage IV patients. The median values at various stages in present study was comparable to the studies of **Pleskow et al [23]**,

Safi et al [24], and **Ferrone et al [25]** while the median values shows a large amount of discrepancy with median values of studies **Jiang et al [22]**, **Kim et al [26]** and **Dong et al [21]**.

It was because of criteria of inclusion of subjects, large sample size, geographic distribution and present study had only included resectable pancreatic cancers.

It was observed in the present study that mean survival rate of patient decreased as preoperative value of CA 19-9 increased. Hence preoperative serum CA 19-9 has a prognostic significance. The results of present study were comparable to **Berger et al [27]**, **Ferrone et al [25]** and **Waraya et al [28]**.

In present study, percentage of change in serum CA 19-9 value after resection or radio/chemo-therapy was considered with survival of patient. It was observed that mean survival of patient was more if postoperative serum CA 19-9 value decreased to less than 50% of original preoperative value. These findings were consistent with other studies like **Saad et al [29]**, **Stemmler et al [30]** and **Reni et al [31]**. The correlation between all the studied definitely suggest there is significance in change of serum CA 19-9 level post-operatively with survival of patients.

In present study the sensitivity was 87.50 % while specificity was 50% for diagnosis of pancreatic carcinoma. The sensitivity was comparable to other studies which are **Haglund et al [32]**, **Cwik et al [33]**

and Ma et al [34]. While the specificity is showing discrepancy. This is because in the study of Haglund et al [32], there was a large sample size. In comparison with Cwik et al [33], the problem was large sample size and he considered only malignant lesions while in present study sample size is small and both benign and malignant conditions were considered. In the study Ma et al differs from present study because he didn't consider any benign conditions only healthy individuals and patients with pancreatic cancer were considered [34].

Gall bladder carcinoma/cholangiocarcinoma- Qin et al [35] study included 35 cases of cholangiocarcinoma and 92 cases of benign biliary disease. Present study includes 15 cases of cholangiocarcinoma and 3 cases of benign biliary disease. The mean age for cholangiocarcinoma in study of Qin et al [35], was 60.37 years while in the present study the mean age was 58.86 years. Both the studies are comparable. Qin et al, 2014 studied patients with Male to Female (M: F) ratio of 1.8:1. In present study the male to female ratio was 1.6: 1 which is quite comparable [35].

In present study 15 cases were studied and it was observed that when serum CA 19-9 level was less than 300 u/ml median survival was 23.25 months and when CA 19-9 was more than 300 u/ml median survival decreased to 10.25 months. Similar observation was made in study of Harder et al [36]. Thus, it is quite comparable.

In **present study** sensitivity was 80% and specificity was 66.66% while in study of Qin **et al 2014** it has sensitivity of 77.41% and specificity was 84.78% for cholangiocarcinoma [35]. While in present study, sensitivity was comparable to afore mentioned study at 77.41 %. But specificity of present study was less as compared to study done by Qin et al [35]. The reason for this being, specificity takes into account 'true negative' and 'false positive'. In present study the 'false positive' was more because, it considered only 3 cases of benign disease of gall bladder which were choledocholithiasis while 92 cases were studied in study of Qin et al [35], 2014 and they included bile duct stricture, choledocholithiasis, cholecystic poly and chronic cholecystitis. Present study observed an increase in serum ca 19-9 level in benign disease of gall bladder. Mean value of serum CA 19-9 in benign disease in present study was 28.66 while it was 13.38 in Qin et al [35], 2014. As a result specificity in present

study was less as compared to Qin et al [35], 2014, mainly as type of benign cases considered were different.

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